UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/993,045	11/13/2001	Timothy R. Brazelton	286002021300	8147

28120 7590 09/09/2004

ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 09/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/993,045	BRAZELTON ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2004* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *22-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6/7/04* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The response and the declaration under 35 USC § 1.132 submitted 6/7/04 have been entered. Claims 1-34 are pending, however, claims 22-34 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 1-21 are under current examination. No claim has been amended.

This application contains claims (22-34) drawn to an invention nonelected without traverse in Paper No. 7. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Declaration

The declaration under 37 CFR 1.132 filed 6/7/04 is defective because it is unexecuted, and thus it is insufficient to overcome the rejection of claims 1-21 based upon 35 USC § 112, 1st paragraph as set forth in the last Office action. However, the subject matter in the unexecuted declaration will be discussed in the following section for the sake of a compact prosecution based on the presumption of a valid declaration submitted in good faith.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-21 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record and following.

In the 6/7/04 response, applicants allege that the Examiner does not cite any art to support the assertion of lack of enablement, and it is inappropriate to require applicants to produce evidence concerning questions raised in the previous Office action, i.e. whether sufficient quantity of new neurons could differentiated to a desired neuronal phenotype, at a proper anatomical location, administered at certain stage of a disease, and sustained presence of these new neurons by the claimed invention.

In response, to conduct the legal test concerning whether the experimentation needed to practice the invention is undue or unreasonable, the Office evaluates the state of the prior art, the relative skill of those in the art, the predictability of the art, and compares such with the breadth of the claims, and the guidance provided in the specification. In the instant case and as indicated in the previous Office action pages 5-10, the claims are directed to treating a neuronal deficiency, preferably congenital disorders due to teratogen or neurodegeneration, the specification teaches that three months after intravenous injection, bone marrow-derived cells were identified in the brain of the injected mice, and some cells expressing neuronal cell surface markers and/or having neuronal cell morphology. Applicants consider this working example as reduction to practice of the claimed method. However, applicants are reminded that the standard for evaluation of the claimed methods is not whether the cells with neuronal identity could be found but whether at least one symptom of the neuronal deficiency has

been ameliorated. It is to this standard, the specification fails to meet the enablement requirement. Further, the specification fails to teach any other route of delivery of cells, and whether such delivery generates sufficient amount of neuronal cells at the site of the lesion, and differentiated to the neuronal phenotype desired for treating a particular deficiency, such that at least one symptom of a congenital disorder such as fetal alcohol syndrome could be ameliorated. The Office then turn to the state of the art and the knowledge of the skilled in the art, citing *Burt et al, Sugaya et al,* and *Galvin et al* to illustrate that the state of the art is silent with respect to using BM stem cells for neuron regeneration, and concluded that based on the levels of the skilled, specific but not general guidance is required. The recited common sense is reflected and fully supported by the cited references. For example, *Burt et al* (Blood 1998;91:2609-16) teach that transplantation of bone marrow-derived cells only slightly improved acute inflammatory infiltration in an EAE model, and failed to improve clinical disease when the treatment is performed in the chronic stage. *Galvin et al* (MJA 2002 ;177:316-8) teach that apparent insufficiencies are lack of primate model to allow potential risks and benefits to be adequately assessed, the lack of sophisticated control of desired neuronal phenotypes and obtaining clinically significant quantities of stem cells. They teach at a post-filing date, "TRIALS IN HUMAN PATIENTS SHOULD NOT BE INITIATED UNTIL: NEUROLOGICAL TESTING SHOWS SIGNIFICANT AND LONG-LASTING FUNCTIONAL RECOVERY AFTER TRANSPLANTATION EXPERIMENTS IN WELL-CHARACTERISED ANIMAL MODELS OF HUMAN CNS DISORDERS". It is noted according to MPEP as pursuant to an enabling disclosure required by 35 U.S.C 112, first paragraph, "DETERMINING ENABLEMENT IS A QUESTION OF LAW BASED ON UNDERLYING FACTUAL FINDINGS". IN RE VAECK, 947 F.2D 488, 495, 20 USPQ2D 1438,

1444 (FED. CIR.1991); ATLAS POWDER CO. V. E.I. DU PONT DE NEMOURS & CO., 750 F.2D 1569, 1576, 224 USPQ 409, 413 (FED. CIR. 1984). One aspect of such factual findings to be considered is "IF LITTLE IS KNOWN IN THE PRIOR ART ABOUT THE NATURE OF THE INVENTION AND THE ART IS UNPREDICTABLE, THE SPECIFICATION WOULD NEED MORE DETAIL AS TO HOW TO MAKE AND USE THE INVENTION IN ORDER TO BE ENABLING. THE "PREDICTABILITY OR LACK THEREOF" IN THE ART REFERS TO THE ABILITY OF ONE SKILLED IN THE ART TO EXTRAPOLATE THE DISCLOSED OR KNOWN RESULTS TO THE CLAIMED INVENTION. ... ACCORDINGLY, WHAT IS KNOWN IN THE ART PROVIDES EVIDENCE AS TO THE QUESTION OF PREDICTABILITY". (MPEP 2164.02, 03) It is noted that in *In re Marzocchi,* the court states "IN THE FIELD OF CHEMISTRY GENERALLY, THERE MAY BE TIMES **WHEN WELL-KNOWN UNPREDICTABILITY OF CHEMICAL REACTIONS WILL ALONE BE ENOUGH TO CREATE REASONABLE DOUBT** AS TO ACCURACY TO **BROAD STATEMENT** PUT FORWARD AS ENABLING SUPPORT FOR CLAIM; THIS WILL ESPECIALLY BE THE CASE WHERE STATEMENT IS, ON ITS FACE, CONTRARY TO GENERALLY ACCEPTED SCIENTIFIC PRINCIPLES, ETC" *(In re Marzocchi and Horton, 169 USPQ 367 CCPA1971)*. The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). When instant claims read on a method for the treatment of any neuron deficiency associated with any congenital or degenerative disease, a doubt is reasonable in view of the levels of the skilled artisans in the prior and post-filing date illustrated in the cited references. Furthermore, the Office has provided numerous teachings to establish the state of the art and the levels of those skilled artisans to indicate the doubt is reasonable. Thus, it is applicants' duty to provide sufficient teaching to enable the claimed invention.

It is noted that in the declaration submitted 6/7/04, applicants provide further experimental data showing that by *intravenous* administration of BM stem cells,

functional correction is observed in a mouse model of *Pakinson's Disease*. This declaration is not sufficient to overcome the rejection because it is defective. Assuming the declaration will be perfected, the specification and the declaration still fails to support the full scope of the claimed invention because the claims encompasses administration by any route, while only intravenous delivery has been used in the declaration and prior art of record (such as Hess et al, and Chen et al); only a Parkinson's disease model was provided while the claimed invention encompasses congenital disorders. To this end, the response fails to address the following issue raised in the previous Office action.

> Fetal alcohol syndrome (FAS) is a congenital disorder caused from embryo alcohol teratogen exposure. FAS is characterized by retarded growth, various abnormalities of the central nervous system, and characteristic abnormalities of the face and head. So far, there is no report on record that such disorder could be treated by any medication or stem cell transplantation... They [Burt et al] concluded that only in the absence of glial scarring and irreversible neuronal injury, the transplantation might be beneficial (e.g. abstract). In the FAS disease, wherein the permanent and irreversible neuronal damage has caused before the birth, thus, it is highly unpredictable whether the insignificant amount of new neurons derived from the transplantation of bone marrow-derived cells would reverse or ameliorate any symptom of FAS in light of the teaching of Burt et al.

In view of above considerations, the specification and the presume perfected declaration fail to provide an enabling disclosure to support full scope of the claims.

Applicants submitted post-filing publications of Hess et al and Chen et al as support for enablement disclosure. However, it is noted both references studied in a brain ischemic model, not congenital neuron deficiency. *Hess et al* illustrated intravenously administered bone marrow cells are incorporated into the vasculature in

the ischemic zone, but did not show any therapeutic effect. Chen et al illustrated certain beneficial effects in re-establishing the blocked circulation, but not beneficial effects on congenital neuron disease or neuron degeneration. The disclosure of Six et al is drawn to a different invention, can not be used as support for the instantly claimed invention.

With regard to the arguments directed to the cited references, it is noted that Burt reference is relied upon as a showing that the disease stage is important in the outcome of BM cell transplantation, thus, relevant to evaluating the enablement of instantly claimed invention. To this end, *Sugaya et al* also teach, "RESEARCHERS HAVE SUCCEEDED IN RECOVERING BRAIN FUNCTION IN ADULT ANIMAL MODELS BY TRANSPLANTATION OF STEM CELLS...NONETHELESS, THESE STUDIES DID NOT TAKE INTO ACCOUNT THE *EFFECT OF PATHOLOGICAL CHANGES THAT MAY OCCUR IN THE DISEASED BRAIN AND THAT MAY PREVENT THE NORMAL DIFFERETIATION OR MIGRATION OF STEM CELLS*" (2nd paragraph, right column, page 1894, emphasis added), which indicated that the type and status of the neuronal diseases are important factors for the outcome of stem cell transplantation. *Sugaya et al* concluded, "CLINICAL TRIALS OF STEM CELL TRANSPLANTATION FOR NEUROLOGICAL DISEASES MAY BE AN IMPORTANT EXPERIMENTAL APPROACH BUT MAY TAKE MORE STUDY OVER A LONGER TIME PERIOD FOR ALL TRANSPLANTATION TO BE ESTABLISHED AS A VIABLE THERAPY" (Conclusion, page 1899), which indicated that a few successes in animal models have not translated to the cross-board clinical benefit for any neuron deficiency in humans as instantly claimed. Here, the evidence of lack of enablement for the claims as broadly claimed are clearly taught by the skilled in the art at a time long after the instant filing date, thus, it is applicants duty to provide sufficient and enabling disclosure to support the full scope of the claims.

With respect to the teachings of *Donovan and Gearhart* (Nat 2001 Nov;414:92-97), it is relied upon as evidence that human and mouse cells behave differently in terms of proliferation and differentiation, it is relevant in that aspect, since claims relied on animal models for support of treating human diseases.

With respect to the Sugaya reference, it is relied upon for the teaching of association concerning the pathophysiological environments of individual disease and how that may affect stem cell biology (e.g. the abstract), accordingly even if the entire article is not limited to BM cell transplantation, it is relevant to the claimed invention. Further, multipotent stem cells are repeatedly mentioned throughout the publication (e.g. 1st paragraph, page 1891), which encompasses BM-derived cells. To this end, the teaching of Sugaya et al points to the evidence to the contrary for the broadly claimed invention encompassing treating any neuron deficiency. For example, *Sugaya et al* (CMLS 2003;60:1891-1902) teach "TRANSPLANTATION OF STEM CELLS... DID NOT TAKE INTO ACCOUNT THE EFFECT OF PATHOLOGICAL CHANGES THAT MAY OCCUR IN THE DISEASED BRAIN AND THAT MAY PREVENT THE NORMAL DIFFERETIATION OR MIGRATION OF STEM CELLS" (2nd paragraph, right column, page 1894), such conclusion is based on the observation that due to the particular pathological brain environment, even if stem cells are transplanted into the brain of a patient with Alzheimer's disease, these cells may differentiated into astrocytes rather than efficiently produce neurons, and likewise, glial cells rather than neurons for Dawn syndrome (e.g. left column, page 1895).

Concerning immunological reactions, applicants argue that similar rejection problems are faced by surgeons in current clinical organ transplantation, and could be

overcome by the immune suppressants. Applicants go on to argue that the methods are used for the most part in untreatable and debilitating conditions. The arguments are fully considered but found not persuasive because xenotransplantation is rarely seen in clinical transplantation even with the aid of immune suppressants. Further, the scope of the claims is not limited to patients with an untreatable condition. In fact, all the cited references (Burt, Galvin, and Sugaya) regarding neuron regeneration list immune rejection as one of the major barrier for successful stem cell transplantation. The new references submitted by applicants such as *Chen et al* and *Hezz et al* use autologous or syngenic cells via intravenous administration. This evidenced the state of the art and relative skilled in the art. Hence, specific guidance and an enabling disclosure are required to enable the broadly claimed invention.

Accordingly, in view of the state of the art at the time of instant filing date, in view of the quantity of experimentation necessary to achieve a therapeutic effect of the numerous neuronal deficiencies in an individual using bone marrow-derived cells, the lack of guidance provided by the specification as well as the absence of working examples with regard to therapy of neuron deficiency diseases, and the breadth of the claim directed to the use of neuronal stem cells in humans, it would required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-10, 13-21 stand rejected under 35 U.S.C. 102(e) as being anticipated by *Sanchez-Ramos et al* (US 2002/0146821, now USP 6,528,245) for reasons of record and following.

Applicants first argue that the disclosure is not enabled.

In response, case law states that anticipation does not require the actual creation or reduction to practice of the prior art subject matter; anticipation requires only an enabling disclosure. *In re Donohue*, 766 F.2d 531, 533 [226 USPQ 619] (Fed. Cir. 1985). A reference may enable one of skill in the art to make and use a compound even if the author or inventor did not actually make or reduce to practice that subject matter. *Bristol-Myers*, 246 F.3d at 1379; see also *In re Donohue*, 766 F.2d at 533.

Applicants then argue that the '821 publication is drawn to a particular type of bone marrow stromal cells cultured in vitro prior to administration directly to the CNS.

In response, both the particular cells and the means of administration (method steps) are encompassed by the claims. Thus, if the instant claims are enabled, the cited art should also be enabled in this aspect.

Therefore, *Sanchez-Ramos et al* anticipate instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 8, 10-12 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Sanchez-Ramos et al* (US 2002/0146821), in view of *Weiss et al* (6,071,889) for reasons of record and those set forth under 35 U.S.C. § 102.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Amy Nelson** can be reached on 571-272-0804. The fax numbers for the organization where this application or proceeding is assigned are **703-872-9306**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within

5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Q. Janice Li
Primary Patent Examiner
Art Unit 1632

QJL
August 30, 2004